REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim Amendments

Claims 1, 2, 8, 9, 13 and 14 have been amended to replace "derivative" with --compound-- and/or to delete the recitation of "solvate". Non-substantive, editorial changes have been made to claims 1, 15 and 16. Claims 17-32 have been cancelled, without prejudice or disclaimer.

Elections/Restrictions

In the second paragraph on page 2 of the Office Action, the Examiner indicates that because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. However, Applicants respectfully remind the Examiner that the requirement set forth on March 31, 2009 was a requirement for an **election of species**, rather than a restriction requirement.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner takes the position that Applicant has not provided sufficient written description for all the claimed pyrazolone derivatives or solvates.

This rejection has been rendered moot by the above-discussed claim amendments.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 17-32 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Specifically, the Examiner indicates that claims 17-32 are incomplete for omitting essential steps.

This rejection has been rendered moot by the above-discussed claim amendments.

Patentability Arguments

The patentability of the present invention over the disclosure of the reference relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ikeda (WO 02/34264, PCT counterpart to U.S. 6,933,310).

The Position of the Examiner

The Examiner takes the position that Ikeda teaches a method of treating amyotrophic lateral sclerosis (ALS) comprising the administration of 3-methyl-1-phenyl-2-pirazoline-5-on, wherein the route of administration of the medicament is not particularly limited, and wherein the medicament can be administered directly to the patient in the form of a pharmaceutical composition. The Examiner asserts that the dose of the medicament can be selected according to various conditions. The Examiner admits that Ikeda does not teach the specific dose regimens which includes holiday periods as disclosed in claim 1-7. However, the Examiner contends that it is within the capability of the ordinary artisan to determine a specific dose regimen for a particular patient.

The Position of Applicants

Applicants respectfully traverse the Examiner's position.

The Examiner has made the general assertion that specific dose regimens and holiday periods are within the capability of one of ordinary skill in the art. However, Applicants respectfully assert that the claimed method, including the recited holiday periods, are unobvious over the prior art.

In order to support this position, Applicants provide herewith a comparison between the case where a drug holiday period of 1 day or more is provided once, twice or more, and the case where such a drug holiday period is not provided, by using an ALS model animal. As demonstrated by the following experimental data, the effect of therapy and/or suppression of progress of ALS or symptoms due to ALS is more excellent in the case where a drug holiday

period of 1 day or more is provided once, twice or more (as in Applicants' claims), as compared with the case where such a drug holiday period is not provided. Therefore, Applicants respectfully assert that the claimed method is not obvious from the teachings of the cited reference.

The details of the experimental comparison, and the results, are provided below.

Discussion of the Methods

1. Animal

Mutant SOD transgenic rats (J. Neurosci., Dec 2001; 21: 9246-9254, copy enclosed), which are used as an ALS model, were used. Genetic analysis was previously carried out, and individuals which are suitable as an ALS model were selected and used for the experiment.

Rats which were 20-weeks old (140 days old) were subjected to administration of the drug.

2. Administration of the drug

Group A: For eight individuals, 3-methyl-l-phenyl-2-pyrazoline-5-on (edaravone) (3 mg/kg) was intravenously administered once a day for two days, followed by a drug holiday period of two days, wherein edaravone was not administered. The schedule of drug administration and drug cessation for Group A is shown in the table below.

Day 1	Day 2	Day 3	Day 4
Drug administration	Drug administration	Drug cessation	Drug cessation

Day 5	Day 6	Day 7	Day 8	------
Drug administration	Drug administration	Drug cessation	Drug cessation	----- ------

This drug administration of two days and drug cessation of two days was repeated until the day before loss of righting reflex.

Group B: For eight individuals, 3-methyl-1-phenyl-2-pyrazoline-5-on (edaravone) (3 mg/kg) was intravenously administered once a day. This drug administration was repeated until the day before loss of righting reflex.

Control Group: For eight individuals, a physiological saline was intravenously administered once a day. This administration was repeated until the day before loss of righting reflex.

3. Evaluation item

The food consumption of one day was measured by measuring the weight of the feeder containing feed by means of a scale for animal.

4. Data processing

For the days after loss of righting reflex, the food consumption of the final measurement day was used.

Discussion of the Results

When ALS proceeds, limb movement disorder and swallowing difficulty occur, and feeding becomes difficult. Therefore, the suppression effect on the reduction of food consumption reflects an effect of therapy and/or suppression of progress of ALS or symptoms due to ALS.

The results of the experiment described above are shown in Fig. 1, which is submitted herewith. The measurements were carried out three times a week from 14 days old (20-weeks old) to 250 days old (35-weeks old).

In all of the groups, a reduction of food consumption was observed on or after 26-weeks old (182 days old). However, the reduction of food consumption in Group A (drug period of two days and drug holiday period of two days) was moderate, and suppression of reduction of food consumption was observed.

Group A showed a significant difference as to the suppression effect of reduction of food consumption on or after 30-weeks old (210 days old), as compared with Group B (daily

administration). Accordingly, Group A showed a significantly excellent effect of therapy and/or suppression of progress of ALS or symptoms due to ALS, as compared with Group B.

Conclusion

The total amounts of edaravone administered are different between Groups A and B. Even if the amount of edaravone per single administration is the same, since edaravone is not administered during the drug holiday period, the total amount of edaravone administered in Group A is less than the total amount of edaravone administered in Group B. Nonetheless, Group A showed a more excellent effect as compared with Group B.

One of ordinary skill in the art would generally expect that a more excellent effect would be obtained in the group with a greater total amount of edaravone administered. However, contrary to this expectation, in the claimed invention, even if the total amount of edaravone administered becomes low, the group with the drug holiday period (Group A) showed a more excellent effect than the group of daily administration (Group B). This advantageous effect would not have been expected by one of ordinary skill in the art.

MPEP 716.02(a) explains that "[e]vidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness." In this case, the Examiner has taken the position that dosing regimens and drug holiday periods are within the capability of one of ordinary skill in the art, and would thus be obvious over the prior art. However, Applicants have provided evidence demonstrating that the claimed method results in unexpected and advantageous properties compared to the method of the prior art.

For the reasons set forth above, it is respectfully asserted that the subject matter of Applicants' claims is patentable over the cited reference. Withdrawal of the above rejection is respectfully requested.

Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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January 21, 2010